THE INFLUENCE OF CAFFEIN ALKALOID ON THE QUALITY AND AMOUNT OF SLEEP

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The data presented here were accumulated during an elaborate series of experiments undertaken with the following five chief purposes in mind.

1. To determine both qualitatively and quantitatively the effect of caffein on a wide range of mental and motor processes by studying the performance of a considerable number of individuals for a long period of time under controlled conditions.

2. To study the way in which this influence is modified by such factors as the age, sex, weight, idiosyncrasy and previous caffein habits of the subjects, and the degree to which it depends on the amount of the dose and the time and conditions of its administration.

3. To investigate the influence of caffein on the general health, on the quality and amount of sleep, and on the food habits of the individuals tested.

4. To inquire into the value and adaptability of a considerable array of simple tests, with a view to their standardization for the purposes of pharmaco-dynamic research.

5. To accumulate data on the effects of practice, fatigue, diurnal variations in efficiency, the physiological limit, individual and sex differences, and various other allied topics growing out of such an extended series of tests on a large number of subjects.

Plan and Procedure

In order to reduce to a minimum distractions and disturbances to which such experiments are usually subjected and to provide for the greatest convenience of the experimenters and the comfort of the subjects, a well lighted and ventilated six-room apartment on the ground floor of a building in a quiet part of the city was equipped as a special laboratory. Sixteen subjects, ten men and six women, were engaged for full time for a period of 40 days, and were required to appear at the laboratory at stated times during the day or

to remain there permanently, as the case might be, and submit themselves to the series of mental and motor tests. These subjects were to abstain from the use of all forms of caffein (coffee, tea, chocolate, cocoa), alcohol, nicotine and all other drugs, as well as from soda fountain drinks containing patent syrups, except in so far as these drugs were prescribed by the director or by the medical assistant. They were also to observe regular hours of eating and sleeping, and to report any unavoidable irregularities in these matters. These conditions were complied with throughout the experiment.

The present study is a report on the second point of the third chief topic. Reports on other topics are ready for publication, and may be expected to appear soon in accessible sources.

The Influence of Caffein on Sleep

Throughout the experiment each subject kept daily records of his general condition of health and spirits throughout the day, indicating in his special "daily health book" any signs of bodily distress or discomfort, such special or general organic, digestive and nervous disturbances as might be noted from time to time, and in general as good an introspective account as possible of his mood and tonus. In addition to stating the character of any symptoms or unusual observations, the time of their appearance and their duration were noted and reference made to any outside factor which might have been responsible for the condition described. This health record was divided into two parts, the first having to do with the day-time hours preceding the evening on which the entry was made, and the second having to do with the night-hours following. This second entry was made on the following morning, immediately on arrival at the laboratory. At this time each individual recorded the approximate number of hours which he had slept during the night and described the quality of his sleep as "better than usual," "ordinary," or "worse than usual." In working up these data the approximate number of hours was accepted as stated. From the point of view of character or quality, an attempt was also made to express the effect of caffein in numerical form. Representing the individual's *usual* quality of sleep by a value of 200; letting the value 100 indicate sleep which, according to the judgment of the individual himself, was *better than usual;* and letting the value 300 represent the quality of sleep which the individual himself judged to be *worse than usual,* tables were compiled from the introspective records

occurring in the daily health books. In the individual averages then as well as in the squad averages, a value of 200 indicates normal sleep; all values less than 200 indicate sleep judged unusually good; while all values larger than 200 indicate impaired sleep.

It will be recognized at once that these measures of sleep quality are only rough and approximate, but it is just as obvious that they are as accurate measurements of the thing in question as can well be secured. The individual himself is the only one who knows anything about his customary sleep quality. In daily life we pass such judgments as those given in the present experiment, and in much the same way, with about the same number of categories. We pronounce ourselves to have slept " well " or " poorly " or " about as usual." Finer distinctions would probably have little or at most exceedingly variable meaning. With respect to the criteria on which such judgments are based there are also considerable individual differences. The number of hours slept through, the number and character of the dreams, the interval after retiring before sleep ensued, the number of times awakened during the night, general feelings of relief or languor after arising, etc., all play their part, no doubt. And the judgment is at best only a secondary one,—that is to say, the quality of sleep is inferred from introspections and observations made during waking moments. In spite of this, few judgments of this subjective character would seem to have higher reliability than the individual's own opinion of the satisfactoriness of his slumber, and when the categories are limited to the three employed here, the judgments are delivered with a high degree of confidence. The reliability of the judgments is moreover emphasized by the consistent conclusions suggested by the various tables.

The statements of number of hours' sleep are at best only approximate, in cases of impaired sleep. When the slumber was not disturbed the figures are more reliable, since all the subjects observed regular hours of retiring and arising. It will not be possible here to compare the individual subjects nor the squad averages with each other, except in so far as the number of hours' sleep on control days is adopted as the normal in each case. A fairly constant average of about 7.5 hours' sleep appears to be the normal for all of the subjects, as is indicated by the records for the week before the caffein doses began, and also by the records for the control days during the caffein experiments.

The records on sleep fall into two general sections, the

first covering 28 days of caffein alkaloid experiments, and the second covering 7 days of experiments with syrups and carbonated water, with and without caffein contents. In the following tables the first column gives the averages for the first week, during which only sugar doses were given to all subjects. The second column gives the averages for the control days during the following three weeks. These two columns may then both be considered as normals. The third column gives the averages for the days on which the dose was either 1 or 2 gr. of caffein, the fourth column the records for the 3 to 4 grain doses, and the fifth column for the 6 gr. doses. The last column gives the final average for all the caffein days (1 to 6 gr. doses). The individual subjects are grouped in squads according to the time at which the dose was taken and according to the distribution of the doses during the month.

Squad I, consisting of subjects 1, 4, 7, and 15, were the control squad, and ran throughout the four weeks on sugar doses only. Nevertheless their records have been averaged as though they had taken the caffein on alternating days, as was the case with squads III and IV. The parenthesis around their averages indicates then that these were not really caffein days, but days on which the caffein squads took the doses indicated at the top of the various columns. The sleep records of the individuals taking caffein may thus be compared with the control records of individuals taking only sugar on the corresponding days. The caffein records are thus trebly checked up,—first by a normal week for all subjects, second by control days for all subjects during the following three weeks, and thirdly by a control squad running throughout the month on sugar doses only.

Squad II, consisting of subjects 8, 12 and 13, took caffein on three days and sugar on the following three days at 10:30 A. M., followed in turn by three days of caffein, and so on throughout the experiment, except that there was only one day available for the 6 grain dose. The 1 to 2 grain records for this squad are the averages of 3 days of 1 grain and 3 days of 2 grain doses. The records for 3 to 4 grains are the averages of three 4 grain days, while the records for 6 grains are not averages but single records.

Squad III took caffein and sugar doses on alternate days throughout the experiment, at the 1 o'clock lunch hour, thus giving two days for each of the 1, 2, 3, 4 and 6 grain doses. Squad IV also alternated caffein with sugar doses throughout

the month, with the same distribution of days as in the case of squad III, the only difference being that the dose was taken in the middle of the afternoon instead of at the lunch hour. Squad III consisted of subjects 3, 9 and 14, while squad IV contained subjects 5, 6, 10, 11 and 16.

Experiments with Caffein Alkaloid

Table I gives the individual averages for quality of sleep during the first four weeks, and also the squad averages, with final averages for the caffein days and a grand average for each column for the three caffein squads.

TABLE I. INFLUENCE OF CAFFEIN ALKALOID ON THE QUALITY OF SLEEP

				CAFFEIN DOSES			
Squad.	*Subjects*	*First Week*	*Control Days*	1 to 2 *gr.*	3 to 4 *gr.*	6 *gr.*	*Caffein Average*
I	1	180	190	(225)	(200)	(150)	(200)
Sugar only	4	200	230	(200)	(200)	(300)	(220)
	7	170	150	(175)	(125)	(100)	(140)
	15	200	230	(225)	(200)	(250)	(220)
	Average.....	187	200	(206)	(181)	(200)	(195)
II							
Morning	8	220	220	250	266	300	273
	12	200	210	200	200	300	233
Caffein 3 days	13	220	190	200	200	200	200
Sugar 3 days							
	Average.....	213	207	216	220	266	234
	3	200	240	275	200	200	225
III	9	220	190	225	200	250	225
With lunch	14	200	230	200	175	200	191
Alternately							
	Average.....	213	220	233	192	217	214
	5	230	200	250	250	300	266
	6	200	190	175	175	250	200
IV	10	220	210	175	225	300	233
Mid P. M.	11	200	210	250	250	200	233
Alternately	16	150	140	150	150	300	200
	Average.....	200	190	200	210	270	226
Grand averages of Squads II, III and IV.....		208	206	216	207	251	224

Table II brings together the averages for each squad, at the same time giving the mean variation of each average and the number of cases from which the average is in each case derived. The table also gives the final averages for the three caffein squads, the mean variation of the three squad averages from this final average, and the total number of cases for each kind of dose. The number of cases depends chiefly on the number of individuals making up the squad,

and in the case of squad II on the fact that 3 grain doses were not administered and that only one 6 grain dose was given.

TABLE II. THE SQUAD AVERAGES FOR CAFFEIN ALKALOID

Squad	*First Week*	*Control Days*	*1 to 2 gr.*	*3 to 4 gr.*	*6 gr.*
I	Av.....187	200	(206)	(181)	...
Sugar only	M. V..... 47	35	35	30	...
	Cases.... 24	28	16	16	...
II					
Caffein 3 days	Av.....213	207	216	220	266
Sugar 3 days	M. V.....40	31	27	33	44
10.30 A. M.	Cases.... 18	30	18	9	3
III	Av.....213	220	233	192	217
With lunch on	M. V..... 31	40	50	15	72
alternate days	Cases.... 18	30	12	12	6
IV	Av.....200	190	200	210	270
mid P. M.	M. V..... 33	49	50	36	39
alternate days	Cases.... 30	50	20	20	9
Final Averages	Av.....208	206	216	207	251
of caffein	M. V.... 6	10	11	10	23
squads	Total cases... 66	110	50	41	18

The data presented in the two preceding tables seem to justify the following conclusions concerning the influence of caffein alkaloid, taken in its pure form, on the quality of sleep.

1. Doses smaller than 6 grains do not cause impairment of sleep, so far as the squad averages indicate. The average M. V. of these squad averages is 38. Although the figures for squad II are larger for all doses of caffein the range is quite within the probable error except for the 6 grain doses where sleeplessness is clearly present (Table II). Squad III shows no sleep impairment whatever, the quality being reported even quite uniformly better on caffein days. Squad IV similarly shows no deterioration in sleep quality until the 6 grain dose is reached, but the falling off at this point (270) is apparent. The final averages of the caffein squads show the rule clearly. Up to the 4 grain doses the sleep quality remains quite constantly about 209, but at 6 grains there is an abrupt falling off to 251 (Table II). Since these figures are the averages of 11 individuals, with daily records covering a period of 28 days, they have high reliability.

2. The influence of the caffein dose depends to a quite appreciable degree on the conditions under which the dose is taken, and especially on the time of day, the contents of the stomach at the time, and the frequency with which the dose is taken. This dependence is indicated by a comparison of the averages for squads II, III and IV.

a. The greatest impairment of sleep quality is found in the case of those taking the doses on successive days (Av. 234), and this is true in spite of the fact that the dose was in these cases taken early in the morning, some four hours before squad IV and two to two-and-a-half hours before squad III. Had the dose been taken later in the day the difference would doubtless have been still greater. It is impossible to say, on the basis of the data at hand, how soon this cumulative effect would be compensated by such processes of adaptation as are well recognized features of drug action.

b. Next to this squad, the greatest sleep impairment is found with the group (Squad IV) taking the caffein dose late in the afternoon, between meals and on an empty stomach (Av. 226).

c. Quite in line with this fact is the further evidence that when the dose is taken along with food substance, as in the case of squad III who took the caffein at the lunch hour, there is absolutely no evidence of sleeplessness. The presence of food substance in the stomach seems not only to retard the action of the drug but to weaken or even completely neutralize its effect, so that the average for squad III (214) is actually better than their own average on control days (220), although this difference, since it is quite within the probable error, is not evidence of genuine superior quality. The lowest value for this squad is at the 1-2 grain doses (233) but this large figure is due solely to the one individual (subject 3, Table I) who reported poor sleep for several nights in succession,—on control days (240) as well as on caffein days.

3. These results are confirmed by a more detailed study of the records of the individuals making up the various squads. Three subjects, 3, 13 and 14 are not affected even by the maximal 6 grain dose. Five remain unaffected until the 6 grain dose is reached, these being subjects 6, 9, 10, 12 and 16. Only three individuals of the total eleven show signs of disturbance before the 6 grain dose is reached,—these being 5 and 8 (who report sleeplessness as soon as the caffein doses begin and show increasing impairment with larger doses) and 11 who reports 250 for 1-2 and for 3-4 grains but did not seem to be disturbed by the 6 grains.

4. The age of the individual, within the limits here reported, —21 to 39 yrs.,—does not seem to influence his susceptibility to the sleep-disturbing effects of caffein. The three individuals who report poor sleep after the minimal doses are 24, 27 and 33 years of age, respectively, averaging 28 years.

The five who were disturbed only by the 6 grains range from 21 to 33 years, averaging 26. The three who are not affected at all are 22, 27 and 39 years old, averaging 29.3 years. The figures thus show no correlation between age and the ease or degree of sleep-disturbance. (See Table III.)

5. Previous caffein habits do not seem to modify the individuals' susceptibility during the experiment. Table III indicates for each subject the coffee or tea drinking habits indulged in before the experiments began, and reveals no uniformity. Individuals who were accustomed to the regular use of caffein-containing beverages are to be found in each group along with those who have never used coffee nor tea, or have used them only occasionally.

6. So far as the present experiment is concerned, no sex differences in susceptibility are disclosed. Four of the subjects in the caffein squads were women. Of these two were affected by minimal doses, one by maximal doses only, and one not at all. Of the men, two were not affected at all, four were affected by the maximal dose only, and one by the minimal.

7. The only factor which correlates closely with susceptibility is weight. Table III shows this correlation clearly. The average weight of those who are affected by the minimal doses is only 120 pounds. The average weight of those who are affected, but only by the maximal dose, is 149 pounds, while the average weight of the three individuals who are not affected at all is 176 pounds. That is to say,—the greater the body weight of the individual the greater the immunity to the sleep-disturbing influence of caffein. The two slightest subjects, 5 and 11, are in the susceptible group, while the heaviest woman and the two heaviest men are in the immune group. The relation between body-weight and the action of drugs in a medicinal way is a well-recognized principle of pharmacology; and it is interesting to find such close confirmation of the principle in these introspective sleep records. It means simply that, when a fixed dose is administered, the heavy or large individual receives relatively a smaller dose per unit of tissue, and the influence of the drug is correspondingly reduced. Age and sex differences in susceptibility to drugs are probably in many cases not true age or sex differences, but differences based on variations in weight or size. A given amount of caffein, for instance, should be expected to produce greater sleep disturbances in a child than in an adult, not so much because of the child's immaturity as

because of the fact that he receives a larger dose per unit of tissue.

Table III presents the classification of the eleven caffein subjects according to their susceptibility, giving at the same time their age, weight and caffein habit.

TABLE III. INDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY

Type	*Subject*	*Age*	*Weight*	*Caffein Habits*
1. Reacted to minimal Doses	8	24	144	Used regularly
	5	33	105	Used regularly
	11	27	110	Abstainer
Average.....		28	120	
2. Reacted to maximum doses only	12	24	160	Used regularly
	9	21	130	Abstainer
	6	33	125	Used regularly
	10	28	157	Occasionally
	16	24	174	Used regularly
Average.....		26	149	
3. No reaction	13	22	175	Used regularly
	3	39	159	Abstainer
	14	27	193	Occasionally
Average.....		29.3	176	

TABLE IV. EFFECT OF CAFFEIN ON AMOUNT OF SLEEP

Squad	*1st Week*	*Control*	*1 to 2 gr.*	*3 to 4 gr.*	*6 gr.*	*Caffein Average*
I. Sugar only.....	7.45	7.40	(7.50)	(7.75)	(7.67)	(7.55)
II. Three day periods.	7.13	7.63	7.46	7.57	7.07	7.37
III. With lunch.....	7.43	7.47	7.57	7.33	6.40	6.90
IV. Mid P. M.....	7.20	7.46	7.38	7.00	6.30	6.88
Average of Squads II, III and IV—Caffein....	7.25	7.52	7.47	7.30	6.59	7.05

Table IV gives the squad averages of the approximate number of hours' sleep, as well as the final average for the three caffein squads. The figures indicate hours and decimal parts of an hour. The indications here thoroughly bear out the conclusions based on the judgments of sleep quality. The control squad (I) shows little variation as the experiment proceeds, the average amount of sleep being uniformly about 7.5 hours. Squad II, taking caffein in the morning, proceeds in much the same way until the 6 grain dose is given, when the time drops to about 7 hours,—a loss of half an hour sleep. The amount of sleep for squad III, taking dose with lunch, does not diminish appreciably until the 6 grain dose is given, when the earlier average of 7.4 hours abruptly drops to 6.4 hours,—a loss of one hour. The figures for squad IV, taking dose in the afternoon, between meals, drops off .5 hour at the 3 to 4 grain doses, and still another .5

hour at the 6 grain dose. Comparing the caffein average with the control average, squads III and IV lose on the whole, for 1 to 6 grain doses, .6 of an hour. While squad II averages, for the whole range of doses, a loss of only .3 of an hour. The grand average of the caffein squads shows a slight tendency to fall off for the small doses, with an abrupt loss of .7 of an hour at the 6 grain dose; while the grand average for the total range of doses (1 to 6 grains) shows a loss of half an hour, the figure falling from 7.5 hours on control days to 7.0 hours. The individual records show nothing new, and are consequently not published here.

Influence of Syrups, with and without Caffein, on the Quality of Sleep

This experiment covered one week. On two days, no dose at all was given; and on two days, soda fountain syrup containing no caffein was served with carbonated water. On the remaining three days, which were, however, scattered throughout the week, varying amounts of the syrup were given, served with the carbonated water as before, but containing caffein alkaloid (1.2 grains per glass). On one day, 1 glass was taken; on another, 3 glasses; and on the third day, 5 glasses. In all cases the drink was taken in the middle of the afternoon. When the large amounts were taken the drinks were distributed over a period of 2 or 2.5 hours. When the small amounts were taken, the three o'clock hour was chosen for the drink. In this experiment, 12 subjects were used, all of whom had taken part in the previous experiment. No squad division was made. The days on which no dose was taken (called "blank days" in the table), served as control days for the whole group.

Representing as before, the *normal* quality of sleep by the value 200, letting 100 represent sleep introspectively judged as *better than usual,* and 300 sleep judged as *worse than usual,* the following table results from the week's experiment on the 12 subjects. The figure for "blank days" is thus an average of 12 records on each of 2 days,—an average of 24 cases. The figure for "syrup days" is an average, in the same

TABLE V. INFLUENCE OF SYRUPS, WITH AND WITHOUT CAFFEIN.

Character of the dose	SLEEP QUALITY *Average*	*M. V.*	HOURS SLEEP *Average*
Blank days	179	54	7.48
Plain syrup, with carbonated water	208	23	7.69
Syrup, with caffein—			
1 glass (1.2 gr.)	180	30	7.42
3 glasses (3.6 gr.)	209	49	7.16
5 glasses (6.0 gr.)	250	60	6.75
Syrup, with caffein, average	213	46	7.11

way, of 24 cases; while each of the "caffein" figures is an average of 12 records.

The results of this experiment completely confirm the conclusions presented in the first section. The "blank days" have a good average quality (179), but no better than that for the day on which the dose consisted of one glass of syrup containing 1.2 grains of caffein. The 3.6 grain dose of caffein results in a poorer quality of sleep than that on the "blank days," but no poorer than that reported on the days on which the same amount of plain syrup was taken (3.6 gr. caffein, 209; plain syrup, 208). Moreover both these figures are approximately ordinary sleep (200). But on the days on which the drink contained 6 grains of caffein there is clear evidence of sleep impairment (250). This is just the point at which the doses of pure caffein alkaloid produced marked signs of sleep disturbance. The average for the three caffein days (1 to 6 gr.) is poorer than that for the plain syrup days (caffein 213, syrup 208), while the average for "blank days" is better than either of these two (179).

The reports of approximate amount of sleep point in the same direction. The "blank days," the plain syrup days and the 1.2 gr. caffein day all yield the well-established normal of about 7.5 hours of sleep. The average after the 3.6 gr. caffein dose appears to be only slightly less, being 7.16, a loss of about .25 hour. But after the 6 grain dose there is an abrupt falling off, the average being only 6.75 hours, a loss of .75 hour as compared with the normal amount. Not only in their relative amounts, but in absolute magnitude as well, the figures for sleep quality and for amount of sleep, in this second section, correspond closely to the figures yielded by the experiments reported in the preceding section on the effects of pure caffein doses.

It should be remarked that in no case did the subjects know the nature of the dose which they were taking at the time. The only indications they had throughout the experiment were based on the after-effects of the drug. In *Section 1,* each subject received a capsule daily, this capsule sometimes containing caffein in amount known only to the director of the experiment, and at other times only sugar of milk. The control capsules were varied in size, as were, of necessity, the caffein capsules. In *Section 2,* the subjects knew only that they were taking soda-fountain drinks. There was said to be a slight variation in the taste from time to time; but this was supposed, by the subjects, to be due to the degree to which the syrup had been mixed with the carbonated water,

to its temperature, etc. The disturbing factors of suggestion, interest, excitement and unequal introspective attention were thus effectually avoided.

Summary

By way of summary we may say,—Small doses of caffein alkaloid (1 to 4 grains), taken either in the pure form or accompanied by small amounts of syrup, do not produce appreciable sleep disturbance except in a few individual cases. Doses larger than these (6 grains, in the present experiment), induce marked sleep impairment with most subjects, though even here a few individuals show complete resistance to its effects. The effects are greatest when the dose is taken on an empty stomach or without food substance, and when it is taken on successive days, so as to permit of cumulative effect. The effect of the drug does not seem to depend on the age, sex, or previous caffein habits of the individual, but varies inversely with increase in body weight. These conclusions hold both for the quality and for the amount of sleep.